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Hypertension

Evaluation of the Extent and Duration of the "ABPM Effect" in Hypertensive Patients

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OBJECTIVES The goal of this study was to test and quantify the extent and duration over time of a possible pressor effect due to ambulatory monitoring.

BACKGROUND The use of ambulatory blood pressure monitoring has provided a method of blood pressure (BP) assessment that compensates for some of the limitations of office values. While a "white-coat" pressor effect on conventional measurements has been defined and frequently used for the improved evaluation of hypertensive patients, there has not been clear indication that the ambulatory technique could also influence BP.

METHODS We studied 538 mild-to-moderate hypertensive patients (233 men), 54.2 ± 14.2 (mean ± SD) years of age. Blood pressure and heart rate were measured at 20-min intervals during the day and at 30-min intervals at night for 48 consecutive hours, and physical activity was simultaneously evaluated at 1-min intervals with a wrist actigraph. One-third of the patients were evaluated twice or more times.

RESULTS In both treated and untreated hypertensive patients evaluated for the first time, results indicate a statistically significant ($p < 0.001$) reduction during the second day of monitoring as compared with the first in the diurnal mean of systolic and diastolic BP, but not in heart rate or physical activity. This pressor effect remains statistically significant for the first 6 h to 8 h of monitoring independently of gender, days of the week of monitoring or number of antihypertensive drugs used by the treated patients. The nocturnal mean of BP was, however, similar between both days of sampling. This "ambulatory monitoring effect" was not observed when the patients were evaluated after the same sampling scheme for the second or successive times three months apart.

CONCLUSIONS Ambulatory monitoring for 48 consecutive hours reveals a statistically significant pressor response that could reflect a novelty effect in the use of the monitoring device for the first time. This effect has marked implications in both research and clinical daily practice for a proper diagnosis of hypertension and evaluation of treatment efficacy by the use of ambulatory monitoring. (J Am Coll Cardiol 2002;40:710–7) © 2002 by the American College of Cardiology Foundation

Blood pressure (BP) determined casually in the physician's office has been commonly used to diagnose hypertension and to evaluate treatment efficacy (1,2). In chronic hypertensive patients, however, the correlation between the BP level and target organ damage, cardiovascular risk, and long-term prognosis is closer for ambulatory blood pressure monitoring (ABPM) than for clinical measurements (3). Another advantage of ABPM is that it allows a better characterization of the patient's BP during his everyday activities. Ambulatory BP monitoring seems particularly useful for defining the efficacy of antihypertensive medication in clinical trials (4). There are, however, some problems associated with ABPM. Apart from its relatively high cost, tolerability of the technique has been discussed as a possible limitation, mostly because ABPM could induce modest sleep disturbances (5). Moreover, there seems to be low individual reproducibility of the circadian profile in BP by repeated ABPM performed on the same patients (6), although results again show clear advantages of ABPM over office values in terms of reproducibility (7).

So far, a large majority of studies have been performed with ABPM for 24 h. Definitions of "normal" ABPM (8), criteria for diagnosis of hypertension (1,2,9) and assessment of antihypertensive therapy (4) have, thus, been established from data gathered over a single 24-h span. While a "white-coat" pressor effect associated with conventional or even self-measurements has been defined and frequently used ever since for the improved evaluation of hypertensive patients (10), there has not been a clear indication that the ABPM technique could also influence BP in patients who use a somehow sophisticated, expensive and unusual device for the first time. If that should be the case, 24 h could be insufficient for a proper evaluation of the circadian variation in BP (6,11–14). With the objective to test and quantify the extent and duration over time of a possible ABPM pressor

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Abbreviations and Acronyms

ABPM = ambulatory blood pressure monitoring
ANOVA = analysis of variance
BP = blood pressure
DBP = diastolic blood pressure
HR = heart rate
SBP = systolic blood pressure

effect, we have assessed the day-to-day variations in BP and physical activity in patients with mild-to-moderate essential hypertension sampled for 48 consecutive hours.

METHODS

Subjects. We studied 538 patients (233 men and 305 women), 54.2 ± 14.2 years of age (range, 22 to 88 years), with diagnoses of mild-to-moderate essential hypertension, according to the recent World Health Organization–International Society of Hypertension classification (2). Among those, 190 patients (35.3%) were not receiving any treatment at the time of their first evaluation by ABPM. All patients received medical care at the Hypertension and Vascular Risk Unit, Hospital Clínico Universitario, Santiago de Compostela, Spain. Shift workers and patients with either "white-coat" hypertension, according to the definitions provided by the Joint National Committee VI (1) and the World Health Organization–International Society of Hypertension (2), severe arterial hypertension, secondary arterial hypertension, cardiovascular disorders other than essential hypertension, or obstructive sleep apnea were excluded from analysis.

BP assessment. The systolic blood pressure (SBP) and diastolic blood pressure (DBP), and heart rate (HR) of each patient were automatically measured every 20 min during the day (7:00 AM to 11:00 PM) and every 30 min during the night for 48 consecutive hours with a SpaceLabs 90207 (SpaceLabs Inc., Redmond, Washington) device. Due to this sampling scheme, ABPM always starts on Monday, Wednesday, or Friday. In order to keep a possible "white-coat" effect to a minimum, only the first BP measurement was performed at the medical setting to validate the proper functioning of the ABPM device. Patients are systematically reevaluated by ABPM in our unit three months after either starting therapy, changing or increasing the number of drugs, or modifying the time or dose of medication. Accordingly, among the subjects participating in the study, 161 were studied two or more times, always three months apart. Subjects were assessed while adhering to their usual diurnal activity (8:00 AM to 11:00 PM for most)-nocturnal sleep routine. They were instructed to go about their usual activities with minimal restrictions but to follow a similar schedule during the two days of ABPM. No person was hospitalized during monitoring. Blood pressure series (a total of 40) were eliminated from analysis when the subjects showed an irregular rest-activity schedule during the two days of sampling, an odd sampling with spans of >3 h without BP measurement, or a night resting span <6 h or >12 h.

The clinical evaluation of this oscillometric monitor according to the standards published by the Association for Advancement of Medical Instrumentation and the British Hypertension Society has been previously established (15). The BP cuff was worn on the nondominant arm with cuff size determined by upper arm circumference at each study visit. Ambulatory blood pressure monitoring always began between 10:00 AM and noon. During monitoring each subject maintained a diary listing the times they went to bed at night, woke in the morning, and ate meals; exercise and unusual physical activity; and events and mood/emotional states that might affect BP. The results presented herein are based on a total of 734 protocol-correct 48-h BP time series collected from the 538 patients.

Actigraphy. The patients wore a MiniMotionLogger actigraph (Ambulatory Monitoring Inc., Ardsley, New York) on the dominant wrist to monitor physical activity every minute at the time of ABPM. This compact (about half the size of a wrist watch) device functions as an accelerometer. The clock time of the actigraph and the ABPM device were always synchronized through their respective interfaces with the same computer. The mean activity for the 5 min before each BP reading was then calculated for analysis, according to previous studies in this area (16).

Statistical methods. Each individual's clock hour BP, HR, and activity values were first re-referenced from clock time to hours before and after awakening from nocturnal sleep, according to the information obtained from actigraphy. This transformation avoided the introduction of bias due to differences among subjects in their sleep/activity routine (12). Blood pressure and HR time series were then edited according to conventional criteria to remove measurement errors and outliers (17). Because activity is not normally distributed, analyses for this variable were done before and after logarithmic transformation. The conclusions from both analyses were practically identical, and, therefore, activity is expressed in original units because this can be more meaningful for those using the same or comparable devices.

The circadian rhythm of BP, HR, and activity for the first and second days of ABPM was objectively assessed by population multiple-component analysis (18), a method applicable to nonsinusoidal-shaped hybrid time series data (time series of data collected from a group of subjects) consisting of values distributed at equal or unequal intervals. The circadian rhythm parameters thus obtained were compared between consecutive days of ABPM by a nonparametric paired test developed to assess differences in parameters derived from population multiple-components analysis (18). Hourly means of each variable were compared between days by *t* test corrected for multiple testing using Holm's procedure (19,20). Average differences for the first 4 h of measurement between the first and the second days of

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ABPM were compared by two-way repeated measures analysis of variance (ANOVA) among groups of treated and untreated patients evaluated for the first or successive times, divided as a function of gender, day of the week of monitoring, and number of antihypertensive drugs used for treatment.

RESULTS

The circadian rhythm of SBP, DBP, HR, and activity in untreated hypertensive patients measured for the first time by ABPM, established separately for data sampled on the first and second days of a 48-h consecutive ABPM span, is depicted in Figure 1. Results indicate a statistically significant BP reduction during the second day of ABPM as compared with the first ($p < 0.001$ for the comparison of the 24-h mean). This reduction is statistically significant, after correction for multiple testing, in both SBP and DBP for the 4 h to 5 h immediately after the start of ABPM (2 h to 3 h after awakening in most subjects; shadowed area in Fig. 1). For the first 4 h of measurement (Table 1), the second day of ABPM is characterized by an average reduction of 5.7 and 4.2 mm Hg in SBP and DBP, respectively, as compared with the first day of monitoring ($p < 0.001$ for both variables). Individually, this "ABPM pressor effect" was documented in 74% of the untreated patients. Because the effect lasts just a few hours, the nocturnal means of BP were similar between both days of sampling (differences of −0.15 and 0.12 mm Hg for SBP and DBP; $p > 0.564$). Thus, the reduction in 24-h mean during the second day of measurement is, although significant, rather small (about 1.5 mm Hg). As a consequence of the decrease in BP during diurnal activity but not during nocturnal resting hours, 32% of the patients characterized as dippers during the first day of ABPM became nondippers in the second day of measurement. Despite the highly significant differences in BP between consecutive days of ABPM, there were no differences in daily (24-h), diurnal, nocturnal or even any of the 24 hourly means in HR or physical activity between the first and the second days of monitoring (bottom graphs of Fig. 1).

For hypertensive patients receiving antihypertensive medication at the time of their first evaluation by ABPM, results indicate a statistically significant BP reduction during the second day of monitoring for about 6 to 7 consecutive hours (shadowed area in graphs on the top of Fig. 2), although the effect seems to be significant for about the first 9 h of measurement. The average BP difference between days of sampling for the first 4 h of ABPM was 6.8 mm Hg for SBP and 4.9 mm Hg for DBP (Table 1). This "ABPM effect" is documented in 72% of the treated patients in this study. There was no significant difference in nocturnal mean nor in any of the hourly means during nocturnal rest between the two days of ABPM (Fig. 2). Results indicate, however, a significant reduction of 4.5 mm Hg in the diurnal mean of SBP (2.4 mm Hg for DBP). About 36% of the dipper patients became nondippers during the second day of measurement. Results further indicate the absence of any significant difference between consecutive days of monitoring in HR or physical activity (bottom graphs of Fig. 2).

The comparison between consecutive days of ABPM in patients studied for the second or successive time indicates the lack of any statistically significant difference in daily, diurnal, nocturnal or hourly means of BP, HR and activity ($p > 0.232$ in all cases; Fig. 3). The larger, but not significant, difference (after correction for multiple testing) between days of sampling in BP was obtained at about 3 h after awakening, that is, close to the time when ABPM started for most patients. This difference could represent the expected "white-coat" effect at the office.

Because the "ABPM effect" seems to persist for at least the first 4 h of sampling, we evaluated possible confounding factors in this pressor effect by comparing the average differences for the first 4 h of measurement between the first and second days of ABPM among groups of patients evaluated for the first or successive times, divided as a function of gender, day of the week of monitoring and number of antihypertensive drugs used for treatment. Results indicate a significant "ABPM effect" for every subgroup of patients who were evaluated for the first time (first two columns in Table 1). Although the effect seems to be consistently higher among treated patients, there is no statistically significant difference in the extent of BP change between any subgroup of treated and untreated patients (last column in Table 1). Differences are, however, significant in SBP and DBP for almost every subgroup studied when one compares treated and untreated patients studied for the first time with those evaluated for the second or successive times (fourth column in Table 1). The nonsignificant difference in DBP among the three groups being compared for ABPM starting on Wednesday becomes significant ($p = 0.045$) when the third group (second ABPM) is compared with the composite of the first two (first ABPM, independently of treatment). The comparison by two-way ANOVA of the "ABPM effect" between days of the week of sampling indicates the lack of differences for each of the three groups studied ($p > 0.354$ for both SBP and DBP). Similarly, there is no statistically significant difference in the extent of the "ABPM effect" as a function of the number of antihypertensive drugs used by the treated patients ($p > 0.747$).

DISCUSSION

Hypertensive patients seem to exhibit a greater day-to-day variability in BP than normotensive subjects (11). Although most studies assessing the circadian BP profile have used 24-h ABPM, as a compromise with practicality, monitoring over at least 48 h has been shown to present advantages in the analysis of BP variability (11–13), diagnosis of disease (14) and evaluation of a patient's response to treatment (13). The individualized estimation of rhythm characteristics become more reliable; new end points are obtained, such as the circadian period, that cannot usually be estimated from

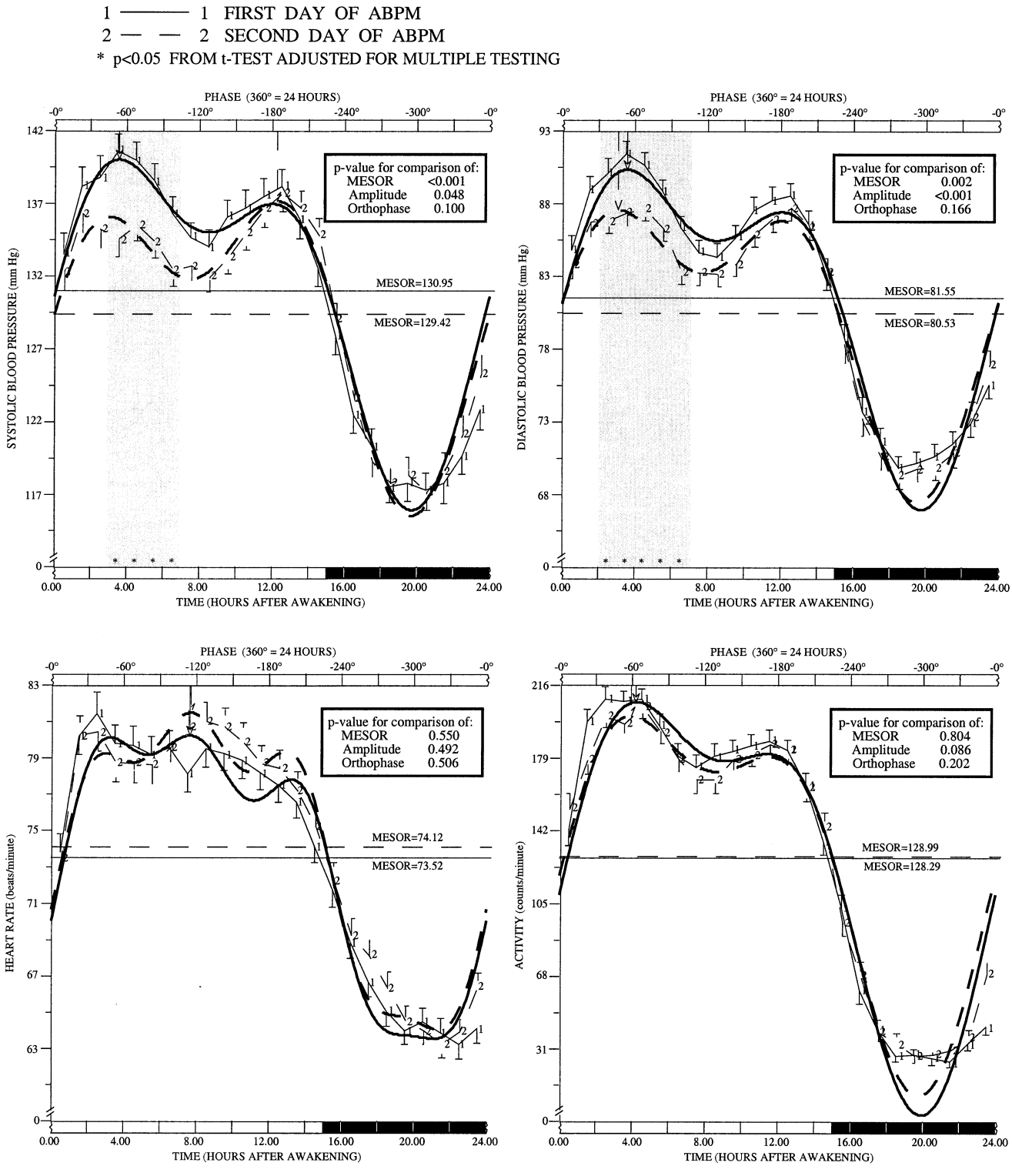

Figure 1. Differences in the circadian pattern of systolic and diastolic blood pressure, heart rate, and activity between the first and the second day of a 48-h ambulatory blood pressure monitoring (ABPM) in untreated patients with mild-to-moderate hypertension measured for the first time. Each graph shows the hourly means and standard errors of data collected during the first **(continuous line)** and second **(dashed line)** day of monitoring. The **nonsinusoidal-shaped curve** represented for each day corresponds to the best-fitted waveform model determined by population-multiple-component analysis (with corresponding characteristics given in the **table below each graph**). The **arrows** descending from the upper horizontal axis point to the circadian orthophase (rhythm's crest time) for each day of monitoring.

Table 1. Blood Pressure Differences for the First 4 h of Measurement Between the First and Second Days of a 48-h ABPM in Patients With Mild-to-Moderate Hypertension

Group/Variable	1st ABPM		2nd and Successive ABPM	p Value for Comparison	
	Untreated	Treated		All Groups	First 2 Groups
All subjects, n of series	190	348	196		
SBP	5.7 ± 0.7	6.8 ± 0.7	1.6 ± 0.6	<0.001	0.277
DBP	4.2 ± 0.5	4.9 ± 0.4	2.0 ± 0.5	<0.001	0.318
Men	89	144	86		
SBP	6.3 ± 1.0	5.9 ± 1.0	2.5 ± 0.9	0.027	0.820
DBP	4.3 ± 0.7	4.3 ± 0.6	2.4 ± 0.7	0.036	0.987
Women	101	204	110		
SBP	5.2 ± 0.9	7.4 ± 0.9	0.81 ± 0.9	<0.001	0.115
DBP	4.2 ± 0.6	5.4 ± 0.6	1.68 ± 0.7	<0.001	0.213
ABPM starting on Monday	77	119	72		
SBP	6.0 ± 1.1	8.9 ± 1.1	1.6 ± 1.1	<0.001	0.080
DBP	4.4 ± 0.7	6.0 ± 0.6	2.0 ± 0.8	<0.001	0.093
ABPM starting on Wednesday	61	117	65		
SBP	4.4 ± 1.1	6.2 ± 1.1	2.4 ± 0.9	0.031	0.281
DBP	3.9 ± 0.8	4.1 ± 0.8	2.1 ± 0.8	0.132	0.867
ABPM starting on Friday	52	112	59		
SBP	6.8 ± 1.2	5.2 ± 1.2	0.7 ± 1.2	0.011	0.424
DBP	4.5 ± 1.0	4.6 ± 0.8	1.9 ± 0.8	0.035	0.913
Patients receiving 1 drug		169	76		
SBP		6.6 ± 0.9	2.5 ± 0.9	0.004	
DBP		4.8 ± 0.6	1.0 ± 0.7	<0.001	
Patients receiving 2 drugs		104	48		
SBP		5.6 ± 1.2	1.5 ± 1.5	0.044	
DBP		4.1 ± 0.8	2.6 ± 1.0	0.155	
Patients receiving 3 or more drugs		75	40		
SBP		8.9 ± 1.7	−0.5 ± 1.6	<0.001	
DBP		6.2 ± 1.0	0.6 ± 1.2	<0.001	

All values given in mean ± SE.
ABPM = ambulatory blood pressure monitoring; DBP = diastolic blood pressure; SBP = systolic blood pressure.

24-h records (21). Thus, previous results suggested that ABPM done only for 24 h may be too short to characterize accurately the features of the day-night variation in BP, including the precise period of that variation (21).

Results from this study indicate that BP is significantly affected by the novelty of wearing an ABPM device for the first time. This "ABPM effect" increases BP on the average by a significant 7 mm Hg and 4 mm Hg for SBP and DBP, respectively, for the first 4 h of measurement. This pressor effect, individually documented in about 73% of all hypertensive patients evaluated by 48-h ABPM in this study, persists as statistically significant for up to 9 h after patients start wearing the device. Due to the lack of differences in nocturnal BP values, the effect on the 24-h mean is lower than the differences between consecutive days of monitoring shown for the diurnal mean of BP (above 4 mm Hg for SBP). This increase in BP is not related to any change in HR or physical activity (Figs. 1 and 2). Further evidence that the ABPM effect reflects a pressor response to the novelty of the device comes from the results represented in Figure 3. Differences between consecutive days of ABPM are no longer significant when hypertensive patients are evaluated for the second or successive times. Moreover, the pressor response to ABPM seems to be independent of possible confounding factors such as the use of antihypertensive medication, gender, day of the week of monitoring and number of antihypertensive drugs used for treatment (Table 1).

The significant ABPM effect shown in the first but not in successive BP profiles raises the question of its potential influence on the results from trials designed to evaluate treatment efficacy based on ABPM for only 24 h. Along these lines, the need for a placebo group in clinical trials with ABPM is still under debate. In a study by Mancia et al. (22), administration of placebo for six to eight weeks was accompanied by no change in 24-h, daytime or night-time BP averages. However, SBP during the initial 4 h of the monitoring was slightly but significantly lower after placebo treatment (by 3.1 mm Hg, $p < 0.05$) compared with baseline values. Although the authors did not perform ABPM beyond 24 h, the placebo effect that they though was a consequence of a "white-coat" effect could, indeed, be just an indication of the "ABPM effect" documented in Figures 1 to 3. Because the "ABPM effect" persists for hours after the patient leaves the hospital setting, but it is significantly attenuated with repeated evaluations by ABPM, it cannot be considered as a manifestation of the "white-coat" effect (10).

Another relevant issue is the reproducibility of the differences between diurnal and nocturnal BP in hypertensive patients. Thus, results associating the lack of nocturnal decline in BP (nondipping) with an increase in end-organ

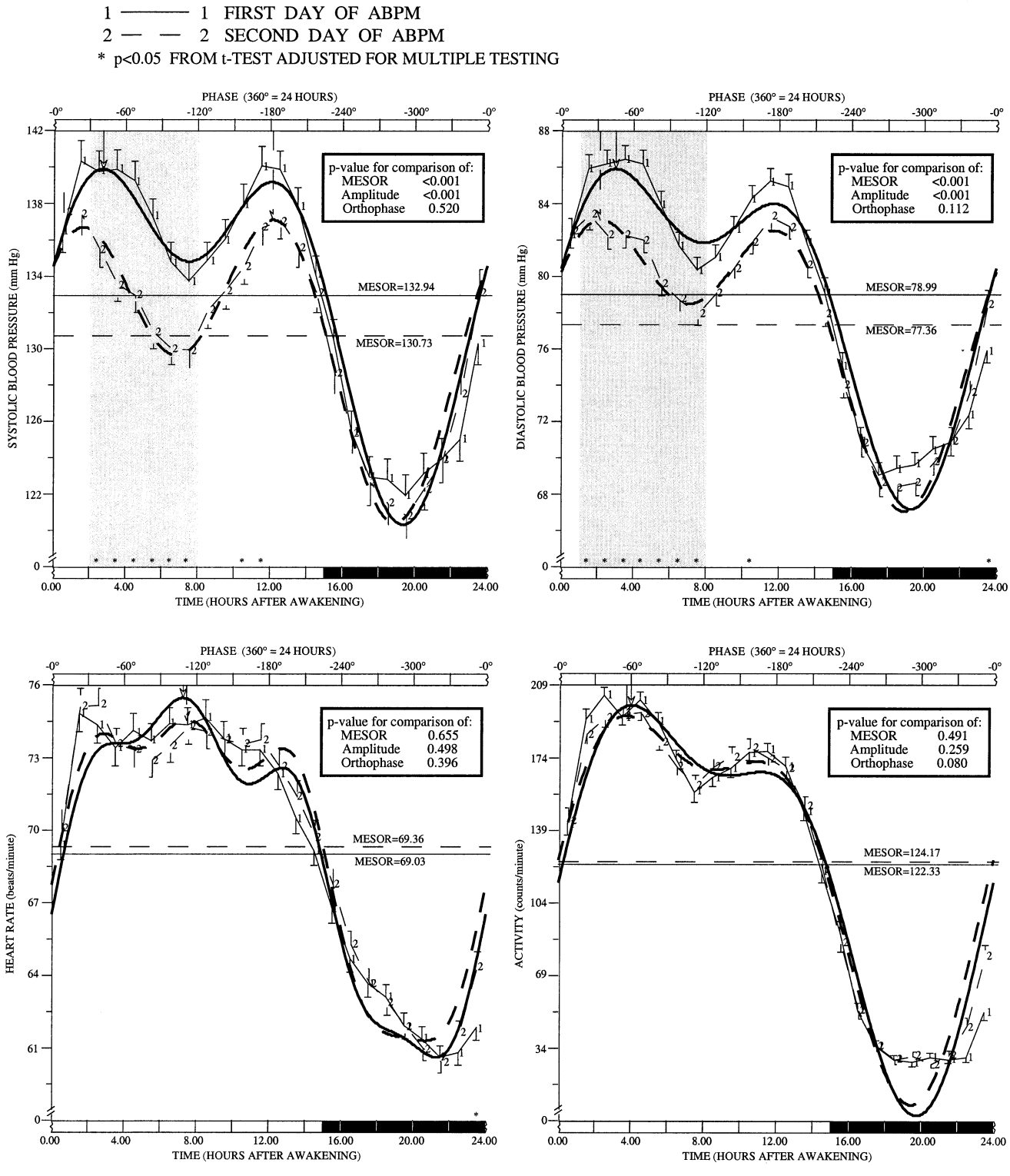

Figure 2. Differences in the circadian pattern of systolic and diastolic blood pressure, heart rate, and activity between the first and the second day of a 48-h ambulatory blood pressure monitoring (ABPM) in treated patients with mild-to-moderate hypertension measured for the first time. Each graph shows the hourly means and standard errors of data collected during the first **(continuous line)** and second **(dashed line)** day of monitoring. The **nonsinusoidal-shaped curve** represented for each day corresponds to the best-fitted waveform model determined by population-multiple-component analysis (with corresponding characteristics given in the **table below each graph**). The **arrows** descending from the upper horizontal axis point to the circadian orthophase (rhythm's crest time) for each day of monitoring.

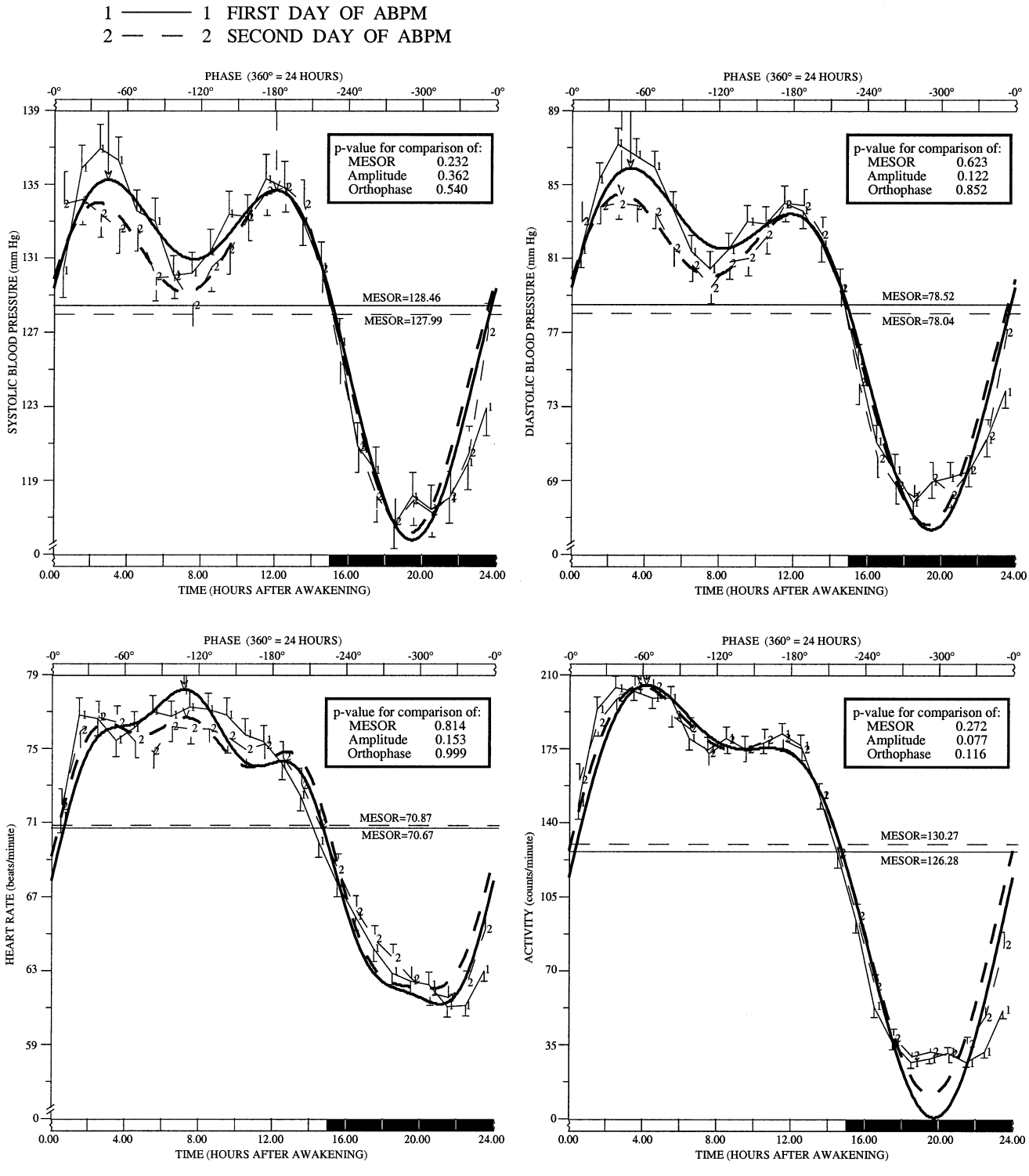

Figure 3. Lack of differences in the circadian pattern of systolic and diastolic blood pressure, heart rate, and activity between the first and the second day of a 48-h ambulatory blood pressure monitoring (ABPM) in patients with mild-to-moderate hypertension measured for the second or successive times. Each graph shows the hourly means and standard errors of data collected during the first **(continuous line)** and second **(dashed line)** session of monitoring, determined three months apart. The **nonsinusoidal-shaped curve** represented for each session corresponds to the best-fitted waveform model determined by population-multiple-component analysis (with corresponding characteristics given in the **table below each graph**). The **arrows** descending from the upper horizontal axis point to the circadian orthophase (rhythm's crest time) for each session of monitoring.

damage and cardiovascular events (3) are still controversial, partly due to the inability to properly reproduce over time the classification of patients into dippers and nondippers (6,23). Along these lines, the pressor effect due to ABPM significantly increases BP during at least half of the diurnal active hours, without modifying the nocturnal BP (Figs. 1 and 2). As a consequence, there is a significant increase in the total number of nondippers when this classification is obtained on the basis of data sampled during the second day of ABPM as compared with the first. The "ABPM effect" could, thus, provide an underestimation of the real percentage of nondippers among patients with mild-to-moderate hypertension (6).

In summary, the results in Figures 1 to 3 document an ABPM effect on BP independent of any change in the activity pattern or any apparent modification in HR. The ABPM effect observed during the first few hours of sampling has marked implications in clinical trials for evaluation of antihypertensive medications because this pressor response could lead to some overestimation of the peak effect of the drug and underestimation of the trough:peak ratio. The results further indicate that ABPM for just 24 h may be insufficient for a proper diagnosis of hypertension, evaluation of treatment efficacy and identification of dipping status in relation to target-organ damage.

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